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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S. Au, *et al.*
Serial No.	:	09/587,662
Filed:	:	June 5, 2000
For:	:	METHODS AND COMPOSITION FOR MODULATING DRUG ACTIVITY THROUGH TELOMERE DAMAGE
TC/AU	:	1623
Examiner	:	Josephine Young
Attorney Docket No.	:	TNI 2-006

HONORABLE COMMISSIONER FOR PATENTS

DECLARATION UNDER 37 C.F.R. § 1.132

Declarant, Jessie L.-S. Au, does declare and state that:

1. She received her Doctor of Pharmacy and Doctor of Philosophy degrees from the University of California San Francisco, in 1972 and 1980, respectively. She has been on the faculty of The Ohio State University since 1983, rising to the rank of Full Professor in 1992. She has served on multiple government advisory boards (including, *inter alia*, Experimental Therapeutic Study Section, Pharmacology Study Section and Board of Scientific Counselors of the National Institutes of Health, U.S. Army Breast Cancer Program, Cancer Center Support Grant Review Committee, Manpower Initial Review of the National Cancer Institute). She currently serves on the Clinical Studies Initial Review Committee for the National Cancer Institute. She is also on the Editorial Boards of *Pharmaceutical Research* and *PharmSci*. She received a Research Career Development Award and a Merit Award from the National Cancer Institute, and a Distinguished Scholar Award, the Dorothy M. Davis Chair in Cancer Research, and a Distinguished University Professorship from The Ohio State University. She is a Fellow of the American Association of Advancement of Science and a Fellow of the American Association of Pharmaceutical Scientists. She was Co-director of three research programs (Developmental Therapeutics, Urologic Oncology, Head and Neck Oncology), Director of Translational Research, and Deputy Director of The Ohio State University Comprehensive Cancer Center, one of the then 28 centers in the U.S. that received such designation from the National Cancer Institute.

2. Her research interests and experience are to develop effective cancer chemotherapy, by identifying effective drugs or combinations of drugs, and by identifying the optimal treatment schedules including the dose and treatment duration. Her work in this area has led to the identification of a new treatment for bladder cancer, for which she has received U.S. Patent No. 6,286,513 B1. This new bladder cancer treatment is based on a new treatment schedule using mitomycin C, a drug that has been used for over 25 years. She and her co-inventor discovered that the prior regimen of administering mitomycin C was less than optimal and subsequently found a new treatment regimen that is nearly twice as effective in human patients, as compared to the prior regimen.
3. Similarly, the above-identified patent application teaches a novel method to use existing drugs in a new way.
4. She is an inventor of and co-applicant for the above-identified application.
5. She and her co-inventor have determined that the combined application of a telomere-damaging agent, and an inhibitor of telomerase, causes a synergistic antitumor effect. This synergy was found in four tumor models, representing major types of human cancer, including FaDu, which is a head and neck cancer; PC3, which is a prostatic cancer; SKOV-3, which is an ovarian cancer; and MCF-7, which is a breast cancer. Together, these cancer types account for about 50% of all adult human cancers. Furthermore, telomerase is expressed in 85-90% of human cancer cells, but not in normal somatic cells and telomerase is required for telomere maintenance (Neidle and Kelland, *Anticancer Drug Design*, 14:341-347, 1999). Hence, the present invention should be applicable in a majority of cancer patients.
6. She and her co-inventor discovered that two other reverses transcriptase inhibitors, suramin and pentosan polysulfate (PPS), have telomerase-inhibitory properties and enhance the efficacy of cytotoxic chemotherapy. These studies are described in greater detail in the provisional application entitled, "Inhibition of telomerase activity by suramin, pentosan polysulfate or antisense to human telomerase" (U.S. Provisional Application No. 60/444,061, filed January 31, 2003). These studies identified suramin as an effective inhibitor of telomerase activity in head and neck cancer FaDu, prostatic cancer PC3, and breast cancer MCF-7 cells. Concentrations causing a 50% inhibition of enzyme activity ranged from 1.4 to 2.8 μM, and were similar for intact cells and cellular extracts. Prolonged treatment (7-15 weeks) of cells in monolayer culture with suramin or another reverse transcriptase inhibitor AZT resulted in 34-55% telomere shortening in FaDu cells, and about 30% shortening in PC3 cells. The *in vivo* effectiveness of

suramin as an inhibitor of telomerase activity was evaluated by measuring the telomere length in tumor cells implanted in immunosuppressed mice. A 6-week treatment using twice-weekly doses of 10-mg/kg suramin in FaDu-bearing animals resulted in a gradual shortening of the telomeres of tumor cells over time, with a reduced or eliminated telomere signal in approximately 95% of the cells at week 6. The effects of PPS on telomerase activity was determined in FaDu and SKOV-3 cells, and showed a concentration-dependent inhibition with 50% inhibition at concentrations of approximately 0.6 µg/ml for both cell lines. In other studies in tumor-bearing immunosuppressed mice, we showed that suramin, at telomerase inhibitory concentrations, enhanced the cytotoxicity of various established anticancer agents. This included enhancement of the antitumor effect of paclitaxel and CPT 11 in colon HT 29 tumors, of paclitaxel and gemcitabine in pancreas Hs766T tumors, and of 5-fluorouracil in renal RCC 54 tumors. PPS enhanced the activity of paclitaxel in pancreas Hs766T tumors. These additional findings indicate that reverse transcriptase inhibitors are effective telomerase inhibitors that can enhance the activity of chemotherapy.

7. The ability of yet another telomerase inhibitor, *i.e.*, antisense to the RNA component of human telomerase (antisense hTR), to enhance the antitumor activity of multiple anticancer drugs with different action mechanisms was studied in human pharynx FaDu cells. Cells were transfected with antisense hTR and the antisense expression by IPTG treatment (referred to as Antisense+IPTG) were obtained, as described in the

TABLE 1

Enhanced activity of vincristine, docetaxel and cisplatin by antisense hTR. Cells were treated with drugs for 48 or 96 hours and drug effect was measured by the sulforhodamine assay as described in Example 8 in the application. Mean ± SD of two to four experiments, three to six replicates per data point for each experiment, are shown.

		Drug concentration that produced 50% cytotoxicity			
	Time (hours)	FaDu	FaDu+IPTG	Sense+IPTG	Antisense+IPTG
Vincristine (nM)	48	4.77 ± 1.09	4.90 ± 0.62	5.00 ± 1.03	2.52 ± 0.06 [a]
Vincristine (nM)	96	2.58 ± 0.31	2.51 ± 0.13	2.31 ± 0.65	1.19 ± 0.47 [a]
Docetaxel (nM)	48	15.43 ± 3.82	14.01 ± 2.35	25.02 ± 7.01	7.12 ± 0.99 [a]
Docetaxel (nM)	96	2.20 ± 0.33	2.22 ± 0.40	2.30 ± 0.40	1.75 ± 0.37 [a]
Cisplatin (mcM)	96	1.27 ± 0.25	1.32 ± 0.23	1.17 ± 0.09	0.95 ± 0.17 [a]

[a] $P<0.05$, as compared to FaDu, FaDu+IPTG, S+IPTG groups (Student's t – test);
[b] $P<0.05$, as compared to FaDu, FaDu+IPTG groups but no significant difference as compared to S+IPTG group (Student's t – test).

application (Example 7). Several controls were used, *i.e.*, parent FaDu cells (referred as FaDu), parent cells treated with IPTG (referred to as FaDu+IPTG), and cells transfected with sense hTR and treated with IPTG (referred to as Sense+IPTG). Table 1 shows the results. Cells expressing antisense hTR showed an increased susceptibility to vincristine, docetaxel and cisplatin, as compared to the control cells.

8. Based on this data and published reports in this field, it is her expert opinion that the invention disclosed teaches the skilled artisan that the invention likely will work for any cell in which telomerase activity repairs damaged telomeres, such as in cancer, and that no undue experimentation is necessary to practice the invention with other cell types.

9. Based on this data and published reports in this field, it is her expert opinion that the invention disclosed teaches the skilled artisan which compositions are effective as telomere damage-inducing agents and as telomerase inhibitiory agents, and that no undue experimentation is necessary to practice the invention with other telomere damage-inducing agents and other telomerase inhibitiory agents.

10. All statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

FURTHER DECLARANT SAYETH NAUGHT.

Date April 29, 2003

Jessie L.-S. Au

09/587-662 #13 Con't

PDR® entry for

RETROVIR® (GlaxoSmithKline)
(zidovudine)
Tablets
1RETROVIR®
(zidovudine)
Capsules
RETROVIR®
(zidovudine)
Syrup

WARNING

RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS) . PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING RETROVIR AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV).

Tablets: RETROVIR Tablets are for oral administration. Each film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Capsules: RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C Blue No. 2.

Syrup: RETROVIR Syrup is for oral administration. Each teaspoonful (5 mL) of RETROVIR Syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine.

Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY

Mechanism of Action: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5'-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5'-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5'-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed mutations that result in 5 amino acid substitutions (Met41->Leu, A67->Asn, Lys70->Arg, Thr215->Tyr or Phe, and Lys219->Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations with 215 mutation being the most significant.

Cross-Resistance: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for >/=1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62->Val, Val75->Ile, Phe77->116Tyr, and Gln->151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics: ***Adults:*** The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'- *O* -(beta)- *D* -glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second

metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

The extent of absorption (AUC) was equivalent when zidovudine was administered as RETROVIR Tablets or Syrup compared to RETROVIR Capsules.

Table 1. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:plasma ratio *	0.6 [0.04 to 2.62] (n =39)
Systemic clearance (L/hr/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (hr) †	0.5 to 3 (n = 19)
*Median [range].	
† Approximate range.	

Adults with Impaired Renal Function: Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) >/=15 mL/min.

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment *

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1
*Data are expressed as mean ± standard deviation.		

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg

5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION : Dose Adjustment).

Adults with Impaired Hepatic Function: Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION : Dose Adjustment).

Pediatrics: Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (Table 3).

Patients from 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m ^{2} every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION : Pediatrics).

Patients Younger Than 3 Months of Age: Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates </=14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION : Neonatal Dosing .

Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients *

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.68 (0.03 to 3.25) † (n = 38)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

*Data presented as mean ± standard deviation except where noted.

† Median [range].

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth

were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers: **The Centers f r Disease C ntr l and Preventi n recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS: Nursing Mothers).

Geriatric Patients: Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gend r: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet.

Effect of Food on Absorption: RETROVIR may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

Drug Interactions: See Table 4 and PRECAUTIONS : Drug Interactions .

Zidovudine Plus Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Table 4. Effect of Coadministered Drugs on Zidovudine AUC *
Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	up AUC 31%	Range 23% to 78% †	<->
Fluconazole 400 mg daily	200 mg q 8 hr	12	up AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	up AUC 43%	Range 16% to 64% †	<->
Nelfinavir 750 mg q 8 hr × 7 to 10 days	single 200 mg	11	down AUC 35%	Range 28% to 41%	<->
Probenecid 500 mg q 6 hr × 2 days	2 mg/kg q 8 hr × 3 days	3	up AUC 106%	Range 100% to 170% †	Not Assessed
Rifampin 600 mg daily × 14 days	200 mg q 8 hr × 14 days	8	down AUC 47%	90% CI: 41% to 53%	Not Assessed

Ritonavir 300 mg q 6 hr × 4 days	200 mg q 8 hr × 4 days	9	down AUC 25%	95% CI: 15% to 34%	<->
Valproic acid 250 mg or 500 mg q 8 hr × 4 days	100 mg q 8 hr × 4 days	6	up AUC 80%	Range 64% to 130% †	Not Assessed
up = Increase; down = Decrease; <-> = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.					
*This table is not all inclusive.					
† Estimated range of percent difference.					

INDICATIONS AND USAGE

RETROVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Maternal-Fetal HIV Transmission: RETROVIR is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been assessed (see Description of Clinical Studies).

Description of Clinical Studies: Therapy with RETROVIR has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV disease and to delay disease progression in asymptomatic HIV-infected patients.

Combination Therapy in Adults: RETROVIR in combination with other antiretroviral agents has been shown to be superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4 cell counts, and decreasing plasma HIV RNA. The clinical efficacy of a combination regimen that includes RETROVIR was demonstrated in study ACTG320. This study was a multicenter, randomized, double-blind, placebo-controlled trial that compared RETROVIR 600 mg/day plus EPIVIR 300 mg/day to RETROVIR plus EPIVIR plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or death was lower in the triple-drug-containing arm compared to the two-drug-containing arm (6.1% versus 10.9%, respectively).

The complete prescribing information for each drug should be consulted before combination therapy that includes RETROVIR is initiated.

Monotherapy in Adults: In controlled studies of treatment-naive patients conducted between 1986 and 1989, monotherapy with RETROVIR, as compared to placebo, reduced the risk of HIV disease progression, as assessed using endpoints that included the occurrence of HIV-related illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4 cell counts between 200 and 500 cells/mm ^{3} (ACTG016 and ACTG019). A survival benefit for monotherapy with RETROVIR was not demonstrated in the latter 2 studies. Subsequent studies showed that the clinical benefit of monotherapy with RETROVIR was time limited.

P diatric Patients: ACTG300 was a multicenter, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive pediatric patients were enrolled in these 2 treatment arms. The median age was

2.7 years (range 6 weeks to 14 years), the mean baseline CD4 cell count was 868 cells/mm ^{3}, and the mean baseline plasma HIV RNA was 5.0 log $_{10}$ copies/mL. The median duration that patients remained on study was approximately 10 months. Results are summarized in Table 5.

Table 5. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Pregnant Women and Their Neonates: The utility of RETROVIR for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG076) conducted in HIV-infected pregnant women with CD4 cell counts of 200 to 1,818 cells/mm ^{3} (median in the treated group: 560 cells/mm ^{3}) who had little or no previous exposure to RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of RETROVIR during labor and delivery. Following birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV infection in the neonates (based on viral culture from peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

CONTRAINDICATIONS

RETROVIR Tablets, Capsules, and Syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS

COMBIVIR and TRIZIVIR are combination product tablets that contain zidovudine as one of their components. RETROVIR should not be administered concomitantly with COMBIVIR or TRIZIVIR.

The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

Bone Marrow Suppression: RETROVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm ^{3} or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of RETROVIR, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood transfusions, has occurred during treatment with RETROVIR alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

Myopathy: Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of RETROVIR.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering RETROVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with RETROVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY : Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Information for Patients: RETROVIR is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of RETROVIR in women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, that may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with RETROVIR.

RETROVIR Tablets, Capsules, and Syrup are for oral ingestion only. Patients should be told of the importance of taking RETROVIR exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of RETROVIR are unknown at this time.

Pregnant women considering the use of RETROVIR during pregnancy for prevention of HIV-transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and infant exposure to RETROVIR are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with RETROVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Drug Interactions: See CLINICAL PHARMACOLOGY section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

Antir troviral Agents: Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided.

Doxorubicin: Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Overlapping Toxicities: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with

dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK $^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-transmission (see INDICATIONS AND USAGE: Description of Clinical Studies). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received RETROVIR and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to RETROVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease C ntrol and Prevention rec mmend that HIV-infected mothers not breastfeed their infants to avoid risking p stnatal transmission f HIV. Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY : Pharmacokinetics : Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **m thers should be instructed not to breastfeed if they are receiving**

RETROVIR (see Pediatric Use and INDICATIONS AND USAGE : Maternal-Fetal HIV Transmission).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS , DOSAGE AND ADMINISTRATION , INDICATIONS AND USAGE : Description of Clinical Studies , and CLINICAL PHARMACOLOGY : Pharmacokinetics).

Geriatric Use: Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adults: The frequency and severity of adverse events associated with the use of RETROVIR are greater in patients with more advanced infection at the time of initiation of therapy.

Table 6 summarizes events reported at a statistically significant greater incidence for patients receiving RETROVIR in a monotherapy study:

Table 6. Percentage (%) of Patients with Adverse Events * in Asymptomatic HIV Infection (ACTG019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Body as a whole		
Asthenia	8.6% †	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4% †	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%
*Reported in >/=5% of study population.		
† Not statistically significant versus placebo.		

In addition to the adverse events listed in Table 6, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with RETROVIR are shown in Table 7.

Table 7. Frequencies f Selected (Grade 3/4) Lab ratory

Abn rmalities in Patients with Asymptomatic HIV Infecti n (ACTG019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm ^{3})	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm ^{3})	0%	0.5%
ALT (>5 × ULN)	3.1%	2.6%
AST (>5 × ULN)	0.9%	1.6%
Alkaline phosphatase (>5 × ULN)	0%	0%
ULN = Upper limit of normal.		

Pediatric: ***Study ACTG300:*** Selected clinical adverse events and physical findings with a >/=5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m ^{2} 3 times daily compared with didanosine in therapy-naive (</=56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Selected Clinical Adverse Events and Physical Findings (>/=5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears *	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%
*Includes pain, discharge, erythema, or swelling of an ear.		

Selected laboratory abnormalities experienced by therapy-naive (</=56 days of antiretroviral therapy)

pediatric patients are listed in Table 9.

Table 9.: Frequencies of Selected (Grade 3/4) Laborat ry Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	EPIVIR plus RETROVIR	Didanosine
Neutropenia (ANC <400 cells/mm ^{3})	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm ^{3})	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total amylase (>2.5 × ULN)	3%	3%
ULN = Upper limit of normal.		
ANC = Absolute neutrophil count.		

Additional adverse events reported in open-label studies in pediatric patients receiving RETROVIR 180 mg/m ^{2} every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss. The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm ^{3}). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of RETROVIR in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to RETROVIR, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain.

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Ey : Macular edema.

Gastr intestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

N rvous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Sp cial Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urog nital: Urinary frequency, urinary hesitancy.

OVERDOSAGE

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of RETROVIR is 600 mg per day in divided doses in combination with other antiretroviral agents.

Pediatrics: The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m ^{2} every 8 hours (480 mg/m ^{2} /day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

Maternal-Fetal HIV Transmission: The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times per day until the start of labor (see INDICATIONS AND USAGE: Description of Clinical Studies). During labor and delivery, intravenous RETROVIR should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing

through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

Monit ring f Patients: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Dose Adjustment: ***Anemia:*** Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm ^{3} or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Hepatic Impairment: There are insufficient data to recommend dose adjustment of RETROVIR in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since RETROVIR is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring for hematologic toxicities is advised (see CLINICAL PHARMACOLOGY : Pharmacokinetics and PRECAUTIONS : General).

HOW SUPPLIED

RETROVIR Tablets 300 mg (biconvex, white, round, film-coated) containing 300 mg zidovudine, one side engraved "GX CW3" and "300" on the other side. Bottle of 60 (NDC 0173-0501-00).

Store at 15° to 25°C (59° to 77°F).

RETROVIR Capsules 100 mg (white, opaque cap and body with a dark blue band) containing 100 mg zidovudine and printed with "Wellcome" and unicorn logo on cap and "Y9C" and "100" on body. Bottles of 100 (NDC 0173-0108-55) and Unit Dose Pack of 100 (NDC 0173-0108-56).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg zidovudine in each teaspoonful (5 mL). Bottle of 240 mL (NDC 0173-0113-18) with child-resistant cap.

Store at 15° to 25°C (59° t 77°F).

GlaxoSmithKline, Research Triangle Park, NC 27709

December 2001/RL-1040

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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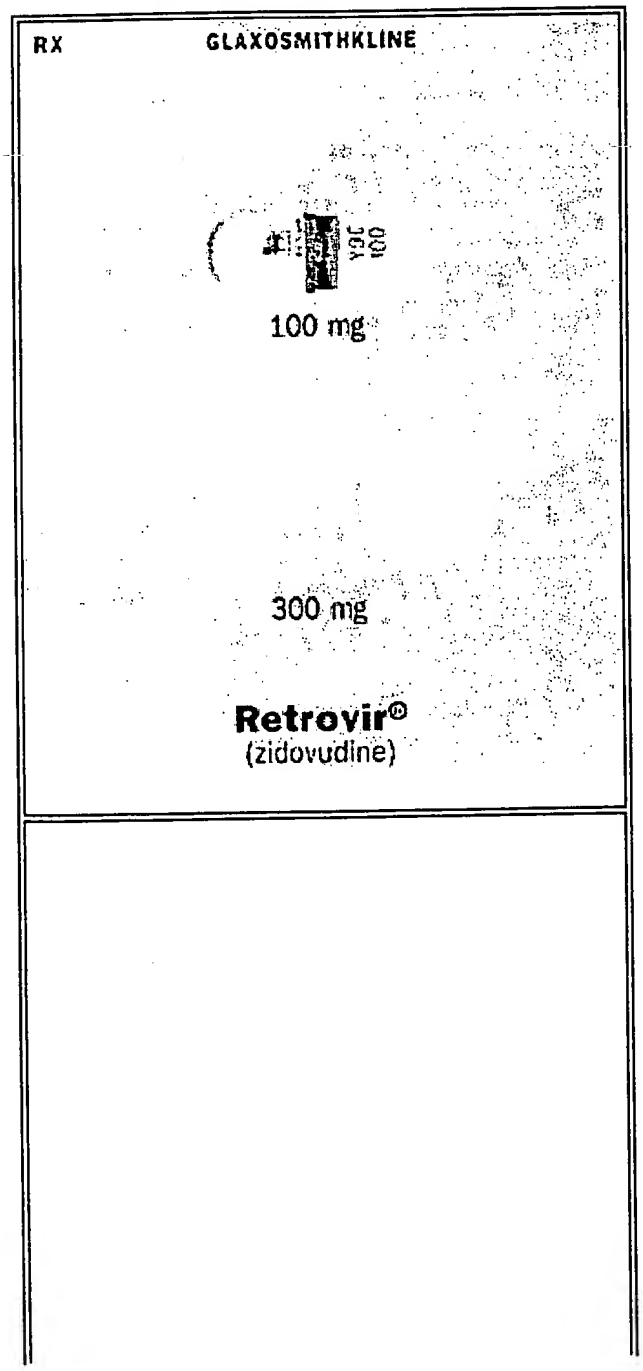
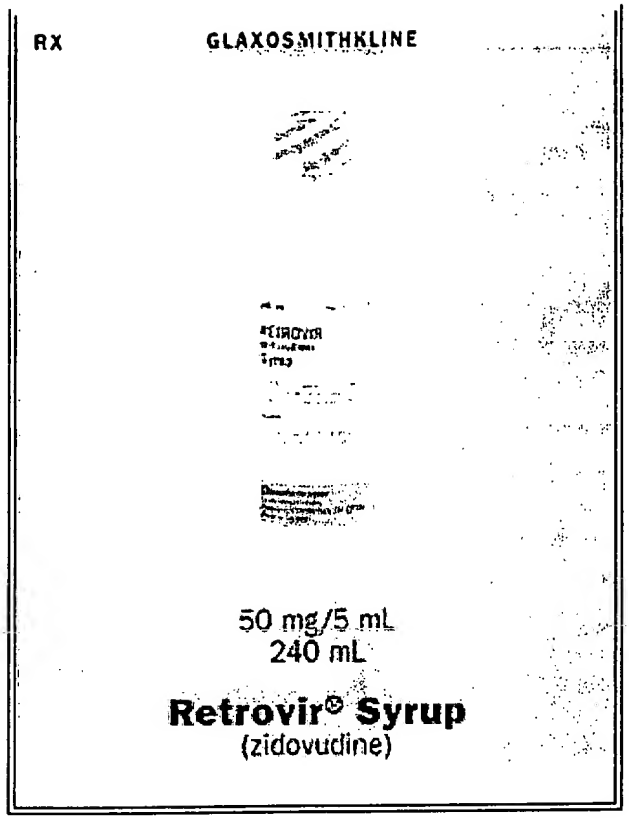




PDR® entry for

RETROVIR® (GlaxoSmithKline)
(zidovudine)
IV Infusion
FOR INTRAVENOUS INFUSION ONLY

WARNING

RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY. LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING RETROVIR AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV). RETROVIR IV Infusion is a sterile solution for intravenous infusion only. Each mL contains 10 mg zidovudine in Water for Injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH to approximately 5.5. RETROVIR IV Infusion contains no preservatives.

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine.

Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY

Mechanism of Action: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5'-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5'-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5'-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL).

The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed mutations that result in 5 amino acid substitutions (Met41->Leu, A67->Asn, Lys70->Arg, Thr215->Tyr or Phe, and Lys219->Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations, with 215 mutation being the most significant.

Cross-Resistance: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for >/=1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62->Val, Val75->Ile, Phe77->116Tyr, and Gln->151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics: ***Adults:*** The pharmacokinetics of zidovudine have been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. Following intravenous (IV) dosing, dose-independent kinetics was observed over the range of 1 to 5 mg/kg. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'- *O* -(beta)- *D* -glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 18% and 60%, respectively, following IV dosing. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose IV administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC.

The mean steady-state peak and trough concentrations of zidovudine at 2.5 mg/kg every 4 hours were 1.06 and 0.12 mcg/mL, respectively.

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in 39 patients receiving chronic therapy with RETROVIR. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of RETROVIR was 0.6.

Table 1. Zidovudine Pharmacokinetic Parameters Following Intravenous Administration in HIV-Infected Patients

Parameter	Mean ± SD (except where noted)

Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 11)
Plasma protein binding (%)	<38
CSF:plasma ratio *	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 (0.8 to 2.7) (n = 18)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 16)
Elimination half-life (hr) †	1.1 (0.5 to 2.9) (n = 19)
*Median [range].	
†Approximate range.	

Adults with Impaired Renal Function: Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) >/=15 mL/min.

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment *

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1
*Data are expressed as mean ± standard deviation.		

The pharmacokinetics and tolerance of oral zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION : Dose Adjustment).

Adults with Impair d Hepatic Function: Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION : Dose Adjustment).

Pediatrics: Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (Table 3).

Patients from 3 Months t 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients >3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m ^{2} every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION : Pediatrics).

Pati nts Younger Than 3 Months of Age: Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates </=14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION : Neonatal Dosing .

Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients *

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.26 ± 0.17 † (n = 28)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n =20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

*Data presented as mean ± standard deviation except where noted.

†CSF ratio determined at steady-state on constant intravenous infusion.

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers: **The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS : Nursing Mothers).

Geriatric Pati nts: Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed

no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet.

Drug Interacti ns: See Table 4 and PRECAUTIONS : Drug Interactions .

Zidovudine Plus Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single oral dose of zidovudine (200 mg) in combination with multiple oral doses of lamivudine (300 mg every 12 hours).

Table 4. Effect of Coadministered Drugs on Zidovudine AUC *

Note:ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Coadministered Drug and Dose	Zidovudine Oral Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	up AUC 31%	Range 23% to 78% †	<->
Fluconazole 400 mg daily	200 mg q 8 hr	12	up AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	up AUC 43%	Range 16% to 64% †	<->
Nelfinavir 750 mg q 8 hr × 7 to 10 days	single 200 mg	11	down AUC 35%	Range 28% to 41%	<->
Probenecid 500 mg q 6 hr × 2 days	2 mg/kg q 8 hr × 3 days	3	up AUC 106%	Range 100% to 170% †	Not Assessed
Ritonavir 300 mg q 6 hr × 4 days	200 mg q 8 hr × 4 days	9	down AUC 25%	95% CI: 15% to 34%	<->
Valproic acid 250 mg or 500 mg q 8 hr × 4 days	100 mg q 8 hr × 4 days	6	up AUC 80%	Range 64% to 130% †	Not Assessed

up = Increase; down = Decrease; <-> = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

*This table is not all inclusive.

†Estimated range of percent difference.

INDICATIONS AND USAGE

RETROVIR IV Infusion in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Maternal-Fetal HIV Transmission: RETROVIR is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been assessed (see Description of Clinical Studies).

Description of Clinical Studies: Therapy with RETROVIR has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV disease at the initiation of therapy and to delay disease progression in asymptomatic HIV-infected patients. RETROVIR in combination with other antiretroviral agents has been shown to be superior to monotherapy in one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4 cell counts, and decreasing plasma HIV-1 RNA. The complete prescribing information for each drug should be consulted before combination therapy that includes RETROVIR is initiated.

Pr gnant Women and Their Neonates: The utility of RETROVIR for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in HIV-infected pregnant women with CD4 cell counts of 200 to 1,818 cells/mm ^{3} (median in the treated group: 560 cells/mm ^{3}) who had little or no previous exposure to RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by intravenous administration of RETROVIR during labor and delivery. Following birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV infection in the neonates (based on viral culture from peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

CONTRAINDICATIONS

RETROVIR IV Infusion is contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS

COMBIVIR® and TRIZIVIR® are combination product tablets that contain zidovudine as one of their components. RETROVIR should not be administered concomitantly with COMBIVIR or TRIZIVIR.

The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

Bone Marr w Suppressi n: RETROVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm ^{3} or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the

use of RETROVIR, which was reversible in most instances, after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood transfusions, has occurred during treatment with RETROVIR alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

Myopathy: Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of RETROVIR.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering RETROVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with RETROVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY : Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Information for Patients: RETROVIR is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of RETROVIR in treating women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, which may exacerbate the toxicity of RETROVIR (see PRECAUTIONS : Drug Interactions). Patients should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with RETROVIR.

Pregnant women considering the use of RETROVIR during pregnancy for prevention of HIV

transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and neonatal exposure to RETROVIR are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with RETROVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Drug Interactions: See CLINICAL PHARMACOLOGY section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

Antiretroviral Agents: Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided.

Doxorubicin: Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in 1 case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Overlapping Toxicities: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Carcin genesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91, and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the

recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK $^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission (see INDICATIONS AND USAGE : Description of Clinical Studies). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received RETROVIR and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antir troviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to RETROVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Contr l and Prevention rec mmend that HIV-infected mothers n t breastfeed their infants to av id risking p stnatal transmission of HIV.

Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY : Pharmacokinetics : Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving RETROVIR** (see Pediatric Use and INDICATIONS AND USAGE : Maternal-Fetal HIV Transmission).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS , DOSAGE AND ADMINISTRATION , INDICATIONS AND USAGE : Description of Clinical Studies , and CLINICAL PHARMACOLOGY : Pharmacokinetics).

Geriatric Use: Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The adverse events reported during intravenous administration of RETROVIR IV Infusion are similar to those reported with oral administration; neutropenia and anemia were reported most frequently. Long-term intravenous administration beyond 2 to 4 weeks has not been studied in adults and may enhance hematologic adverse events. Local reaction, pain, and slight irritation during intravenous administration occur infrequently.

Adults: The frequency and severity of adverse events associated with the use of RETROVIR are greater in patients with more advanced infection at the time of initiation of therapy.

Table 5 summarizes events reported at a statistically significantly greater incidence for patients receiving RETROVIR orally in a monotherapy study:

Table 5. Percentage (%) of Patients with Adverse Events * in Asymptomatic HIV Infection (ACTG 019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Body as a Whole		
Asthenia	8.6%	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastr intestinal		
Anorexia	20.1%	10.5%
Constipation	6.4 † %	3.5%

Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%
*Reported in >/=5% of study population.		
†Not statistically significant versus placebo.		

In addition to the adverse events listed in Table 5, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with oral RETROVIR are shown in Table 6.

Table 6. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection (ACTG 019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm ^{3})	1.8%	1.6%
Thrombocytopenia (platelets <50,000/mm ^{3})	0%	0.5%
ALT (>5 × ULN)	3.1%	2.6%
AST (>5 × ULN)	0.9%	1.6%
Alkaline phosphatase (>5 × ULN)	0%	0%
ULN = Upper limit of normal.		

Pediatrics: ***Study ACTG300:*** Selected clinical adverse events and physical findings with a >/=5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m ^{2} orally 3 times daily compared with didanosine in therapy-naive (</=56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7. Selected Clinical Adverse Events and Physical Findings (>/=5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%

Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose and Throat		
Signs or symptoms of ears *	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%
*Includes pain, discharge, erythema, or swelling of an ear.		

Selected laboratory abnormalities experienced by therapy-naive (</=56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	EPIVIR plus RETROVIR	Didanosine
Neutropenia (ANC<400 cells/mm ^{3})	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm ^{3})	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total amylase (>2.5 × ULN)	3%	3%
ULN = Upper limit of normal.		
ANC = Absolute neutrophil count.		

Additional adverse events reported in open-label studies in pediatric patients receiving RETROVIR 180 mg/m ^{2} every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.

The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients.

Use for the Preventi n of Maternal-Fetal Transmission f HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following

birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm ^{3}). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of RETROVIR in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to RETROVIR, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain.

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosal pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

OVERDOSAGE

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute

overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

Adults: The recommended intravenous dose is 1 mg/kg infused over 1 hour. This dose should be administered 5 to 6 times daily (5 to 6 mg/kg daily). The effectiveness of this dose compared to higher dosing regimens in improving the neurologic dysfunction associated with HIV disease is unknown. A small randomized study found a greater effect of higher doses of RETROVIR on improvement of neurological symptoms in patients with pre-existing neurological disease.

Patients should receive RETROVIR IV Infusion only until oral therapy can be administered. The intravenous dosing regimen equivalent to the oral administration of 100 mg every 4 hours is approximately 1 mg/kg intravenously every 4 hours.

Maternal-Fetal HIV Transmission: The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times per day until the start of labor. During labor and delivery, intravenous RETROVIR should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

Monitoring of Patients: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

D se Adjustment: ***Anemia:*** Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm ^{3} or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal dialysis (CrCl <15 mL/min), recommended dosing is 1 mg/kg every 6 to 8 hours (see CLINICAL PHARMACOLOGY : Pharmacokinetics).

Hepatic Impairment: There are insufficient data to recommend dose adjustment of RETROVIR in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since RETROVIR is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring of hematologic toxicities is advised (see CLINICAL PHARMACOLOGY : Pharmacokinetics and PRECAUTIONS : General).

Meth d of Preparation: RETROVIR IV Infusion must be diluted prior to administration. The calculated dose should be removed from the 20-mL vial and added to 5% Dextrose Injection solution to achieve a concentration no greater than 4 mg/mL. Admixture in biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) is not recommended.

After dilution, the solution is physically and chemically stable for 24 hours at room temperature and 48 hours if refrigerated at 2° to 8°C (36° to 46°F). Care should be taken during admixture to prevent inadvertent contamination. As an additional precaution, the diluted solution should be administered within 8 hours if stored at 25°C (77°F) or 24 hours if refrigerated at 2° to 8°C to minimize potential administration of a microbially contaminated solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

Administration: RETROVIR IV Infusion is administered intravenously at a constant rate over 1 hour. Rapid infusion or bolus injection should be avoided. RETROVIR IV Infusion should not be given intramuscularly.

HOW SUPPLIED

RETROVIR IV Infusion, 10 mg zidovudine in each mL.

20-mL Single-Use Vial, Tray of 10 (NDC 0173-0107-93).

St re vials at 15° to 25°C (59° to 77°F) and protect from light.

Manufactured by Catalytica Pharmaceuticals, Inc.

Greenville, NC 27834

for GlaxoSmithKline, Research Triangle Park, NC 27709

December 2001/RL-1041

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.

RX GLAXOSMITHKLINE

10 mg/mL
20-mL single-use vial

Retrovir® I.V. Infusion
(zidovudine)

PDR® entry for

ZERIT® (Bristol-Myers Squibb Oncology/Vir logy)(stavudine)
ZERIT® (stavudine) Capsules
ZERIT® (stavudine) for Oral S luti n
(Patient Informati n Leaflet Included)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS : PREGNANCY).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

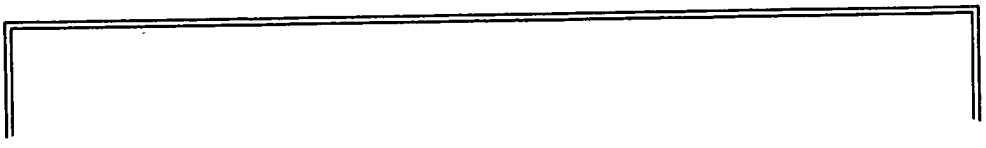
DESCRIPTION

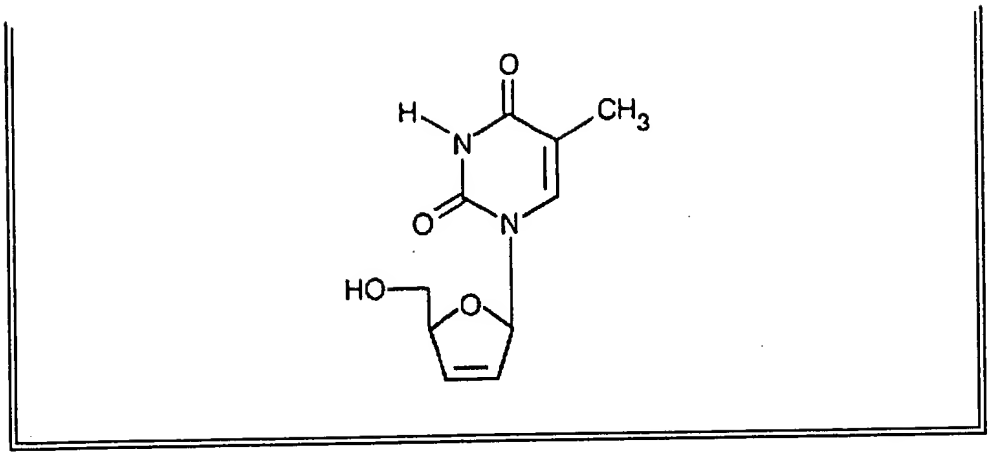
ZERIT® is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the Human Immunodeficiency Virus (HIV).

ZERIT (stavudine) Capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

ZERIT (stavudine) for Oral Solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL stavudine solution upon constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:





Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

MICROBIOLOGY

Mechanism of Action: Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro* . Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate (K_i =0.0083 to 0.032 µM), and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

***In vitro* HIV Susceptibility:** The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit viral replication by 50% (ED_{50}) ranged from 0.009 to 4 µM against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and zalcitabine, respectively, *in vitro* . Stavudine combined with zidovudine had additive or antagonistic activity *in vitro* depending upon the molar ratios of the agents tested. The relationship between *in vitro* susceptibility of HIV to stavudine and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced susceptibility to stavudine have been selected *in vitro* and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV isolates from stavudine-treated patients revealed, in 3 of 20 paired isolates, a 4- to 12-fold decrease in susceptibility to stavudine *in vitro* . The genetic basis for these susceptibility changes has not been identified. The clinical relevance of changes in stavudine susceptibility has not been established.

Cr ss-resistance: Five of 11 stavudine post-treatment isolates developed moderate resistance to zidovudine (9- to 176-fold) and 3 of those 11 isolates developed moderate resistance to didanosine (7- to 29-fold). The clinical relevance of these findings is unknown.

CLINICAL PHARMACOLOGY

Pharmac kinetics: The pharmacokinetics of stavudine have been evaluated in HIV-infected adult

and pediatric patients (Tables 1 and 2). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption - Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.

Distribution - Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/mL. Stavudine distributes equally between red blood cells and plasma.

Metabolism - The metabolic fate of stavudine has not been elucidated in humans.

Excretion - Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

Table 1
Pharmacokinetic Parameters of Stavudine in Adult HIV-Infected Patients

Parameter	Mean ± SD	n
Oral bioavailability	86.4 ± 18.2%	25
Volume of distribution [a]	58 ± 21 L	44
Apparent oral volume of distribution [b]	66 ± 22 L	71
Total body clearance [a]	8.3 ± 2.3 mL/min/kg	44
Apparent oral clearance [b]	8.0 ± 2.6 mL/min/kg	113
Elimination half-life, I.V. dose [a]	1.15 ± 0.35 h	44
Elimination half-life, oral dose [b]	1.44 ± 0.30 h	115
Urinary recovery of stavudine (% of dose) [b]	39 ± 23%	88
[a] following 1 hour I.V. infusion.		
[b] following single oral dose.		

Special Populations:

Pediatric - For pharmacokinetic properties of stavudine in pediatric patients, see Table 2.

Table 2
Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV Exposed or -Infected Pediatric Patients

Parameter	Ages 5 weeks t 15 years	n	Ages 14 to 28 days	n	Day f Birth	n
Oral bioavailability (%)	76.9 ± 31.7	20	ND		ND	
Volume of		21				

distribution [a] (L/kg)	0.73 ± 0.32		ND		ND	
Ratio of CSF:plasma concentrations (as %) [b]	59 ± 35	8	ND		ND	
Total body clearance [a] (mL/min/kg)	9.75 ± 3.76	21	ND		ND	
Apparent oral clearance [c] (mL/min/kg)	13.75 ± 4.29	20	11.52 ± 5.93	30	5.08 ± 2.80	17
Elimination half-life, I.V. dose [a] (h)	1.11 ± 0.28	21	ND		ND	
Elimination half-life, oral dose [c] (h)	0.96 ± 0.26	20	1.59 ± 0.29	30	5.27 ± 2.01	17
Urinary recovery of stavudine (% of dose) [c]	34 ± 16	19	ND		ND	

[a] following 1 hour I.V. infusion.

[b] following multiple oral doses.

[c] following single oral dose.

ND=not determined.

Renal Insufficiency - Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 3). C_{max} and T_{max} were not significantly altered by renal insufficiency. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Table 3
Mean ± SD Pharmacokinetic Parameter Values Single 40-mg Oral Dose of ZERIT

	Creatinine Clearance			
	>50 mL/min (n=10)	**26-50 mL/min (n=5)**	**9-25 mL/min (n=5)**	**Hemodialysis Patients * (n=11)**
CL_{cr} (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
CL/F (mL/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
CL_R (mL/min)	167 ± 65	73 ± 18	17 ± 3	NA
$T_{1/2}$ (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4

CL_{cr} = creatinine clearance.

CL/F = apparent oral clearance.

CL_R = renal clearance.

$T_{1/2}$ = terminal elimination half-life.

NA = not applicable.

*Determined while patients were off dialysis.

Hepatic Insufficiency - Stavudine pharmacokinetics were not altered in 5 non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric - Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See **PRECAUTIONS : Geriatric Use** .)

Gend r - A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Race - A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients (233 Caucasian, 39 African American, 41 Hispanic, 1 Asian, and 4 Other) showed no clinically important differences associated with race.

Drug Interactions - Drug interaction studies have demonstrated that there are no clinically significant interactions between stavudine and the following: didanosine, lamivudine, or nelfinavir.

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT is not recommended.

INDICATIONS AND USAGE

ZERIT, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see Clinical Studies).

Clinical Studies:

Combination Therapy - The combination use of ZERIT is based on the results of clinical studies in HIV-infected patients in double- and triple-combination regimens with other antiretroviral agents.

One of these studies (START 1) was a multicenter, randomized, open-label study comparing ZERIT (40 mg twice daily) plus lamivudine plus indinavir to zidovudine plus lamivudine plus indinavir in 202 treatment-naive patients. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy - The efficacy of ZERIT was demonstrated in a randomized, double-blind study (AI455-019, conducted 1992-1994) comparing ZERIT with zidovudine in 822 patients with a spectrum of HIV-related symptoms. The outcome in terms of progression of HIV disease and death was similar for both drugs.

CONTRAINDICATIONS

ZERIT (stavudine) is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS

1. **Lactic Acid sis/Severe Hepat megaly with Steat sis/Hepatic Failure: Lactic acid sis and severe hepat megaly with steat sis, including fatal cases, have been rep rted with the use f nucle side analogues alone or in c mbinati n, including stavudine and other antiretrovirals.** Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS** : **Pregnancy**).
   Particular caution should be exercised when administering ZERIT to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see **2. Neurologic Symptoms**) might be indicative of lactic acidosis development.
   Treatment with ZERIT should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include heptomegaly and steatosis even in the absence of marked transaminase elevations).
   An increased risk of hepatotoxicity may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea compared to when ZERIT is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. Patients treated with this combination should be closely monitored for signs of liver toxicity.
2. **Neurologic Symptoms:** Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including ZERIT. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.
   Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving ZERIT therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see **ADVERSE REACTIONS**).
3. **Pancreatitis:** Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of ZERIT and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients (See Patient Information Leaflet.):

Patients should be informed of the importance of early recognition of symptoms of lactic acidosis, which include abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness.

Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of ZERIT therapy may be required.

Patients should be informed that an important toxicity of ZERIT is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of ZERIT may be required if toxicity develops.

Caregivers of young children receiving ZERIT therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Patients should be informed that ZERIT is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using ZERIT. They should be advised that ZERIT therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of ZERIT are unknown at this time.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions: Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT is not recommended (see **CLINICAL PHARMACOLOGY** .)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 µg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 µg/mL, with and without metabolic activation). In the *in vivo*

micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Pregnancy: Pregnancy "Category C". Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure). The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ZERIT (stavudine)** .

Pediatric Use: Use of stavudine in pediatric patients from birth through adolescence is supported by evidence from adequate and well-controlled studies of stavudine in adults with additional pharmacokinetic and safety data in pediatric patients.

Adverse events and laboratory abnormalities reported to occur in pediatric patients in clinical studies were generally consistent with the safety profile of stavudine in adults. These studies include ACTG 240, where 105 pediatric patients ages 3 months to 6 years received ZERIT 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received ZERIT 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received ZERIT 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

Stavudine pharmacokinetics have been evaluated in 25 HIV-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg after I.V. or oral administration of single doses and twice-daily regimens and in 30 HIV-exposed or -infected newborns ranging in age from birth to 4 weeks after oral administration of twice-daily regimens (see **CLINICAL PHARMACOLOGY** , Table 2).

Geriatric Use: Clinical studies of ZERIT did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of ZERIT cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ZERIT is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

ADVERSE REACTIONS

Adults: Fatal lactic acidosis has occurred in patients treated with ZERIT in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with ZERIT. Permanent discontinuation of ZERIT should be considered for patients with confirmed lactic acidosis.

ZERIT therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, ZERIT should be discontinued.

ZERIT therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with neurotoxic drug therapy, including didanosine, in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see **DOSAGE AND ADMINISTRATION**). If neuropathy recurs after resumption, permanent discontinuation of ZERIT should be considered.

When ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with ZERIT in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

Selected clinical adverse events that occurred in adult patients receiving ZERIT in a controlled

monotherapy study (Study AI455-019) are provided in Table 4.

Table 4
Selected Clinical Adverse Events in Study AI455-019 [a] (M n therapy)

	Percent (%)	
Adverse Events	**ZERIT (40 mg twice daily) (n=412)**	**zidovudine (200 mg 3 times daily) (n=402)**
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

[a] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received ZERIT (stavudine) in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral naive adult patients receiving ZERIT from two controlled combination studies are provided in Table 5.

Table 5
Selected Clinical Adverse Events in START 1 and START 2 [a] Studies (Combination Therapy)

	Percent (%)			
	START 1		**START 2**	
Adverse Events	**ZERIT+ lamivudine+ indinavir (n=100 [b])**	**zidovudine+ lamivudine+ indinavir (n=102)**	**ZERIT+ didanosine+ indinavir (n=102 [b])**	**zidovudine+ lamivudine+ indinavir (n=103)**
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

[a] START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either ZERIT (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

[b] Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with ZERIT plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 6.

Table 6
Selected Adult Laboratory Abnormalities in Study AI455-019 [a, b]

	Percent (%)	
Parameter	**ZERIT (40 mg twice daily) (n=412)**	**zidovudine (200 mg 3 times daily) (n=402)**
AST (SGOT) (>5.0 × ULN)	11	10
ALT (SGPT) (>5.0 × ULN)	13	11
Amylase (>/=1.4 × ULN)	14	13

[a] Data presented for patients for whom laboratory evaluations were performed.

[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Tables 7 and 8.

Table 7
Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)

	Percent (%)			
	START 1		**START 2**	
Parameter	**ZERIT+ lamivudine+ indinavir (n=100)**	**zidovudine+ lamivudine+ indinavir (n=102)**	**ZERIT+ didanosine+ indinavir (n=102)**	**zidovudine+ lamivudine+ indinavir (n=103)**
Bilirubin (>2.6 × ULN)	7	6	16	8
SGOT (AST) (>5 × ULN)	5	2	7	7
SGPT (ALT) (>5 × ULN)	6	2	8	5
GGT (>5 × ULN)	2	2	5	2
Lipase (>2 × ULN)	6	3	5	5
Amylase (>2 × ULN)	4	<1	8	2

ULN = upper limit of normal.

Table 8

Selected Lab ratory Abn rmalities in START 1 and START 2 Studies (All Grades)

	Percent (%)			
	START 1		START 2	
Parameter	ZERIT+ lamivudine+ indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
SGOT (AST)	42	20	53	20
SGPT (ALT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

Observed During Clinical Practice: The following events have been identified during post-approval use of ZERIT. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to ZERIT, or a combination of these factors.

Body as a Whole - abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see **PRECAUTIONS : Fat Redistribution**).

Digestive Disorders - anorexia.

Exocrine Gland Disorders - pancreatitis [including fatal cases (see **WARNINGS**)].

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver - lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure.

Musculoskeletal - myalgia.

Nervous System - insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see **WARNINGS**).

Pediatric Patients: Adverse reactions and serious laboratory abnormalities in pediatric patients from birth through adolescence were similar in type and frequency to those seen in adult patients (see **PRECAUTIONS : Pediatric Use**).

OVERDOSAGE

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean ± SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

DOSAGE AND ADMINISTRATION

The interval between doses of ZERIT (stavudine) should be 12 hours. ZERIT may be taken without regard to meals.

Adults: The recommended dose based on body weight is as follows:

40 mg twice daily for patients >/=60 kg.

30 mg twice daily for patients <60 kg.

Pediatrics: The recommended dose for newborns from birth to 13 days old is 0.5 mg/kg/dose given every 12 hours (see **CLINICAL PHARMACOLOGY**). The recommended dose for pediatric patients at least 14 days old and weighing less than 30 kg is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.

D sage Adjustment: Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. These symptoms may be difficult to detect in young children (see **WARNINGS**). If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose:

20 mg twice daily for patients >/=60 kg.

15 mg twice daily for patients <60 kg.

If peripheral neuropathy recurs after resumption of ZERIT, permanent discontinuation should be considered.

Renal Impairment - Zerit may be administered to adult patients with impaired renal function with adjustment in dose as shown in Table 9.

Table 9
Recommended Dosage Adjustment for Renal Impairment

Creatinine Clearance (mL/min)	Recommended ZERIT Dose by Patient Weight	
	>/=60 kg	<60 kg
>50	40 mg every 12 hours	30 mg every 12 hours
26-50	20 mg every 12 hours	15 mg every 12 hours
10-25	20 mg every 24 hours	15 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of ZERIT in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients - The recommended dose is 20 mg every 24 hours (>/=60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time

of day on non-dialysis days.

Method f Preparation:

ZERIT (stavudine) for Oral Solution

Prior to dispensing, the pharmacist must constitute the dry powder with purified water to a concentration of 1 mg stavudine per mL of solution, as follows:

1. Add 202 mL of purified water to the container.
2. Shake container vigorously until the powder dissolves completely. Constitution in this way produces 200 mL (deliverable volume) of 1 mg/mL stavudine solution. The solution may appear slightly hazy.
3. Dispense solution in original container with measuring cup provided. Instruct patient to shake the container vigorously prior to measuring each dose and to store the tightly closed container in a refrigerator, 36° to 46°F (2° to 8°C). Discard any unused portion after 30 days.

HOW SUPPLIED

ZERIT® (stavudine) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures:

Table 10
Capsule Strength/Configuration

Product Strength	Capsule Shell Color	Markings on Capsule (in Black Ink)		Capsules per Bottle	NDC No.
15 mg	Light yellow & dark red	BMS 1964	15	60	0003-1964-01
20 mg	Light brown	BMS 1965	20	60	0003-1965-01
30 mg	Light orange & dark orange	BMS 1966	30	60	0003-1966-01
40 mg	Dark orange	BMS 1967	40	60	0003-1967-01

ZERIT® (stavudine) for Oral Solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per mL of solution upon constitution with water. Directions for solution preparation are included on the product label and in the **DOSAGE AND ADMINISTRATION** section of this insert. ZERIT for Oral Solution (**NDC** No. 0003-1968-01) is available in child-resistant containers that provide 200 mL of solution after constitution with water.

US Patent No.: 4,978,655

Storage: ZERIT Capsules should be stored in tightly closed containers at controlled room temperature, 59° to 86°F (15° to 30°C).

ZERIT for Oral Solution should be protected from excessive moisture and stored in tightly closed containers at controlled room temperature, 59° to 86°F (15° to 30°C). After constitution, store

tightly closed containers of ZERIT for Oral Solution in a refrigerator, 36° to 46°F (2° to 8°C). Discard any unused portion after 30 days.

BMS Virology™

Bristol-Myers Squibb Company

Princet n, NJ 08543

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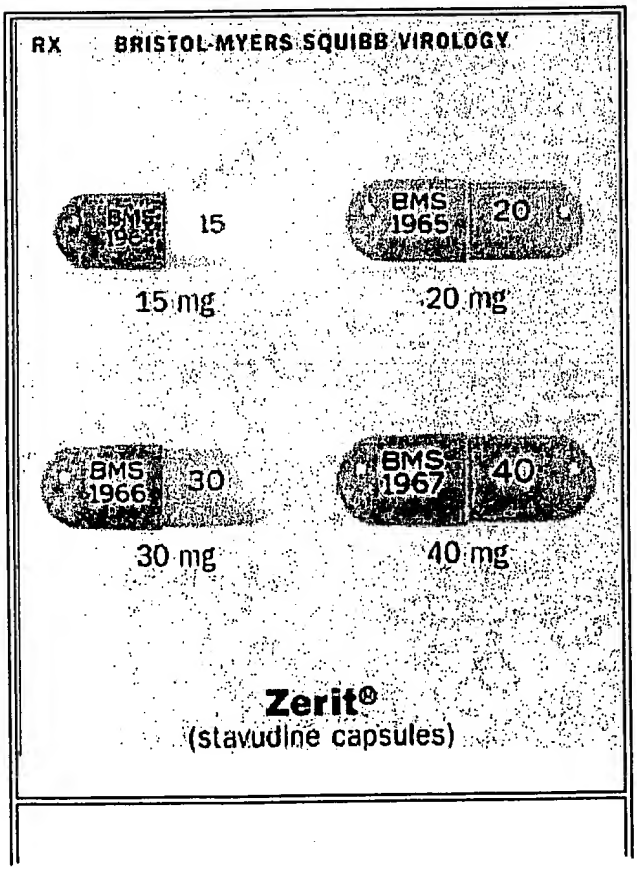
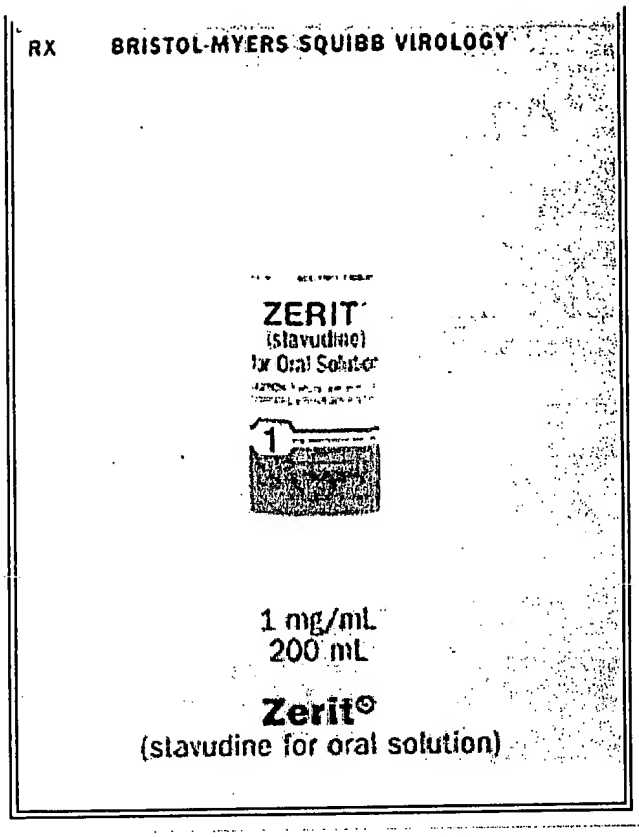
PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.





PATIENT INFORMATION

ZERIT® **Rx ONLY**

(generic name = **stavudine** , also known as **d4T**)

ZERIT® (stavudine) Capsules

ZERIT® (stavudine) for Oral Solution

What is ZERIT ?

ZERIT (pronounced ZER it) is a prescription medicine used in combination with other drugs to treat adults and children who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. ZERIT belongs to a class of drugs called nucleoside analogues. By reducing the growth of HIV, ZERIT helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.

ZERIT will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking ZERIT, you may continue to have HIV-related illnesses, including infections caused by other disease-producing organisms. Continue to see your doctor regularly and report any medical problems that occur.

ZERIT does not prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex and take precautions to prevent others from coming in contact with your blood and other body fluids.

There is limited information on the long-term use of ZERIT.

Wh should not take ZERIT ?

Do not take ZERIT if you are allergic to any of its ingredients, including its active ingredient, stavudine, and the inactive ingredients. (See **Inactive Ingredients** at the end of this leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

How should I take ZERIT ? How should I store it?

Your doctor will determine your dose (the amount in each capsule or spoonful) based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. Take ZERIT exactly as instructed. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. ZERIT may be taken with food or on an empty stomach.

- ***Capsules:*** ZERIT capsules are usually taken twice a day (every 12 hours). Store ZERIT capsules in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- ***Oral solution (for children):*** ZERIT for Oral Solution is taken twice a day (every 12 hours). If your child will be taking ZERIT, the doctor should give you written instructions on how to give this medicine. Before measuring each dose, shake the bottle well. Store ZERIT for Oral Solution in a tightly closed container in a refrigerator and throw away any unused portion after 30 days.

If you have a kidney problem: If your kidneys are not working properly, your doctor may monitor your kidney function while you take ZERIT. Also, your dosage of ZERIT may be adjusted.

What should I do if someone takes an overdosage of ZERIT ?

If you suspect that someone has taken an overdose of ZERIT, get medical help right away. Contact their doctor or a poison control center.

What should I avoid while taking ZERIT ?

Other medicines. Other medicines, including those you can buy without a prescription, may interfere with the actions of ZERIT. You should not use ZERIT in combination with zidovudine (AZT). **Do not take any medicine, vitamin, supplement, or other health preparation without first checking with your doctor.** (Taking ZERIT with other drugs that also may cause peripheral neuropathy may increase your risk of getting this serious side effect.)

Pregnancy: It is not known if ZERIT can harm a human fetus. Also, pregnant women have experienced serious side effects when taking ZERIT in combination with didanosine and other HIV medicines. ZERIT should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking ZERIT.**

Nursing: Because studies have shown ZERIT is in the breast milk of animals receiving the drug, it may be present in human breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **n t** breast-feed to reduce the risk of passing HIV infection to their babies and the potential for serious adverse reactions in nursing infants. Therefore, do not nurse a baby while taking ZERIT.

What are the possible side effects of ZERIT ?

Serious side effects of ZERIT may include:

- **Lactic acid sis** , severe increase of lactic acid in the blood, **severe liver enlargement** , including inflammation (pain and swelling) of the liver, and **liver failure** , which can cause death.
- **Peripheral neuropathy** , a nerve disorder of the hands and feet.

People who take ZERIT along with other medicines that may cause similar side effects may have a higher chance of developing these side effects than if they took ZERIT alone. For example, if you use ZERIT in combination with other drugs (including didanosine, with or without hydroxyurea) that may be associated with liver enlargement, peripheral neuropathy, or pancreatitis, you may be at increased risk for these side effects. Children experience side effects that are similar to those experienced by adults.

Lactic acidosis and severe liver enlargement: Lactic acidosis and severe liver enlargement, including deaths, have been reported among patients taking ZERIT (including pregnant women). ***Symptoms of lactic acidosis may include:***

- ***nausea, vomiting, or unusual or unexpected stomach discomfort;***
- ***fe ling very weak and tired;***
- ***shortness of breath;***
- ***w akness in arms and legs.***

If you notice these symptoms or if your medical condition has suddenly changed, stop taking ZERIT and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital. Women, overweight patients, and those who have had lengthy treatment with nucleoside medicines are more likely to develop lactic acidosis. Your doctor should check your liver function periodically while you are taking ZERIT, especially if you have a history of heavy alcohol use or a liver problem. The combination of ZERIT, didanosine, and hydroxyurea may increase your risk for liver damage, which may be fatal. Your doctor should closely monitor your liver function if you are taking this combination.

Peripheral neuropathy: This nerve disorder is rare, but may be serious. ***Tell your doctor right away*** *if you or a child taking ZERIT (stavudine) has continuing numbness, tingling, burning, or pain in the feet and/or hands.* A child may not recognize these symptoms or know to tell you that his or her feet or hands are numb, burning, tingling, or painful. Ask your child's doctor for instructions on how to find out if your child develops peripheral neuropathy.

Let your doctor know if you or a child taking ZERIT has ever had peripheral neuropathy, because this condition occurs more often in patients who have had it previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may tell you to stop taking ZERIT. In some cases the symptoms worsen for a short time before getting better. Once symptoms of peripheral neuropathy go away completely, ZERIT may be started again at a lower dose.

Pancreatitis: Pancreatitis is a dangerous inflammation of the pancreas. It may cause death. ***Tell your doctor right away if you d v lop stomach pain, nausea, or vomiting. Thes can be signs of pancreatitis.*** Let your doctor know if you have ever had pancreatitis, regularly drink alcoholic beverages, or have gallstones. Pancreatitis occurs more often in patients with these conditions. It is also more likely in people with advanced HIV disease, but can occur at any disease

stage. The combination of ZERIT and didanosine, with or without hydroxyurea, may increase your risk for pancreatitis.

Other side effects: In addition to peripheral neuropathy, the most frequent side effects observed in studies of adults taking the recommended dose of ZERIT were headache, diarrhea, rash, and nausea and vomiting. Other side effects may include abdominal pain, muscle pain, insomnia, loss of appetite, chills or fever, allergic reactions, and blood disorders.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

What else should I know about ZERIT ?

If you have diabetes mellitus: ZERIT for Oral Solution contains 50 mg of sucrose (sugar) per mL.

Inactive Ingredients:

ZERIT Capsules: microcrystalline cellulose, sodium starch glycolate, lactose (milk sugar), and magnesium stearate in a hard gelatin shell.

ZERIT f r Oral Solution: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose (table sugar), and flavoring agents.

This medicine was prescribed for your particular condition. Do not use ZERIT for another condition or give it to others. Keep ZERIT and all other medicines out of the reach of children. Throw away ZERIT when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

This summary does not include everything there is to know about ZERIT. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ZERIT, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

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Princeton, NJ 08543

U.S.A.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

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